REMARKS

Claims 1-21 are pending in the application. Claims 5, 6, 19 and 20 have been withdrawn from consideration.

In the April 12, 2006 Office Action, claim 1 was rejected for obviousness-type double patenting over claims 1 and 17 of copending application 10/766,312. Claims 1-4, 11, and 15-18 were rejected under 35 U.S.C. § 102(b) as anticipated by Li as evidenced by www.dermaxime.com/alcohol.htm. Claims 1, 8, 11 and 12 were rejected under § 102(e) as anticipated by Stemmer. Claims 1-4, 11, and 15-18 were rejected under § 102(e) as anticipated by Heid as evidenced by www.dermaxime.com/alcohol.htm. Claims 1-4, 7, 11, 15-18, and 21 were rejected under 35 U.S.C. 103(a) as being unpatentable over Blaschke in view of both Stemmer and Varadaraj, as evidenced by Swerdlow . Claims 1, 9, 11 and 13 were rejected as obvious over Stemmer in view of Kyle. Claims 1, 8, 10-12 and 14 were rejected as obvious over Stemmer and Kyle further in view of the Sigma catalog and Wierenga. The specific grounds for rejection, and applicants' response thereto, are set forth in detail below.

Rejection for Obviousness-Type Double Patenting

Claim 1 stands rejected for obviousness-type double patenting over claims 1 and 17 of copending application 10/766,312. Applicants respectfully request that this rejection be held in abeyance until an indication of allowability of claim 1.

Rejections Under 35 U.S.C. §102

Applicants address the anticipation rejections in the order set forth in the office action.

Li as evidenced by www.dermaxime.com/alcohol.htm.

Claims 1-4, 11, and 15-18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Li as evidenced by www.dermaxime.com/alcohol.htm. Specifically, the Examiner asserts that Li teaches an RT-PCR method that contains glycerol, and that www.dermaxime.com/alcohol.htm teaches that alcohols are antifoaming reagents. The Examiner therefore concludes that the glycerol in the method described by Li is an antifoaming agent and that the claims are anticipated. Applicants respectfully traverse.

This rejection relies on the www.dermaxime.com/alcohol.htm website to establish that alcohols as a class purportedly are known to be antifoams. As an initial matter, it is highly unlikely that one skilled in the art would regard the www.dermaxime.com/alcohol.htm website as a reliable source of scientific information, since many other pages of this website extol the myriad and unproven virtues of a variety of herbal remedies, and contain many other scientifically unsupportable statements. Applicants respectfully question why the Examiner was unable to identify a publication in a reputable scientific journal that states that alcohols as a class are known to be antifoam reagents. Nevertheless, even if it is assumed for the sake of argument that the website is reliable, the Examiner has misread the cited passage on the website. Thus, the website states that:

> Denatured alcohol is ethyl alcohol, denatured with one or more denaturing agents in accordance with legislation. Alcohol is classed as an alcohol and is used as an anti-foaming, antimicrobial and viscosity decreasing agent as well as a cosmetic astringent and solvent.

(Emphasis supplied) It is clear that the website is referring to ethanol (ethyl alcohol) when it makes the statement about antifoam properties, and is not referring to alcohols *as a class*. Thus the website provides no indication whatsoever that alcohols as a class are known to be antifoams, let alone that glycerol , as used by Li, is an antifoam. This is confirmed by a review of other pages on the website. Thus the page on cetyl alcohol (http://www.dermaxime.com/cetyl-alcohol.htm) states that:

> It is a fatty alcohol, classified as a fatty alcohol and is used as a emulsion stabilizer, fragrance ingredient, opacifying agent, foam boosting and emulsifying surfactant, as well as an aqueous and nonaqueous viscosity-increasing agent

(Emphasis supplied) Thus, the website states that a compound that is unquestionably an alcohol is in fact a foam *booster*, and not an antifoam. Similar statements regarding the foam boosting properties of cetearyl alcohol (http://www.dermaxime.com/ceteary-alcohol.htm), and stearyl alcohol (http://www.dermaxime.com/stearyl-alcohol.htm) can be found on the website. These passages definitively establish that not even the www.dermaxime.com/alcohol.htm website can establish that alcohols as a class can be regarded as antifoams. Rather, it seems to establish that some alcohols act as foam boosters. More particularly, nothing in the website would lead one to believe that glycerol is an antifoam reagent. Without any evidence that glycerol is an antifoam

the rejection here fails because Li fails to teach each and every element of the rejected claims and the rejection should be withdrawn.

Stemmer

Claims 1, 8, 11 and 12 are rejected under § 102(e) as anticipated by Stemmer. Specifically, the Examiner asserts that Stemmer teaches that antifoam reagents can be used in PCR reactions. Applicants respectfully traverse.

It is axiomatic that an anticipatory reference must be enabled. *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003). Nothing in Stemmer would have enabled one skilled in the art to use an antifoam reagent in a PCR reaction because nothing in Stemmer identifies any antifoam reagent that would have worked in a PCR, nor identify an appropriate concentration of that antifoam. Applicants have shown in the instant application that some antifoams substantially inhibit PCR reactions at the concentration required to show antifoam effects, while even for antifoams that are effective without inhibiting activity, too high a concentration of antifoam can be most deleterious. Since Stemmer would not have enabled one skilled in the art to have selected and used an appropriate antifoam reagent without undue experimentation, Stemmer is not an enabling reference, and therefore the rejection is improper and should be withdrawn.

A closer inspection of Stemmer further demonstrates the non-enabling nature of the purported disclosure regarding antifoams. Notably, the reference to antifoam agents occurs in a paragraph that purports to define "physiological conditions" and states that other agents may optionally be added such as divalent cations, metal chelators, nonionic detergents, membrane factions, antifoam reagents and scintillants. Even a cursory review of this disclosure would lead one skilled in the art to conclude that this paragraph is an unreliable source of information regarding PCR reactions. It is well known that PCR reactions are highly sensitive to the nature and concentration of divalent metal cations, yet the paragraph suggests extremely broad ranges (0.001-10mM) for suitable divalent cation concentrations, and indicates that Ca^{2+} would be a suitable divalent cation, even though this would result in no PCR reaction at all.

One skilled in the art would therefore recognize that the cited paragraph would not be a reliable guide to conditions and/or reagents that could be used for a PCR reaction. A paragraph suggesting the inclusion of a chelating agent in a reaction mixture intended for use in a reaction

that would be completely inhibited by a chelating agent would not suggest to the skilled worker the use of an antifoam in a PCR reaction, let alone suggest either the identity of a suitable antifoam, or appropriate concentrations of the antifoam. It is notable that neither the more detailed discussion of PCR reaction conditions at column 17 of Stemmer nor the specific examples of PCR reactions described in Stemmer's Experimental Examples contain any mention whatsoever of antifoam reagents, nor any suggestion that addition of such reagents would be either useful or desirable.

In sum, Stemmer fails to describe to one skilled in the art to select a suitable antifoam reagent that does not inhibit PCR reaction, and further fails to describe a suitable concentration range for this unidentified antifoam reagent. Accordingly, Stemmer is not an enabling reference and cannot anticipate the instantly claimed invention and the rejection should be withdrawn.

Heid as evidenced by www.dermaxime.com/alcohol.htm.

Claims 1-4, 11, and 15-18 were rejected under § 102(e) as anticipated by Heid as evidenced by www.dermaxime.com/alcohol.htm. Specifically, the Examiner asserts that Heid teaches an RT-PCR method that contains glycerol, and that www.dermaxime.com/alcohol.htm teaches that alcohols are antifoaming reagents. The Examiner therefore concludes that the glycerol in the method described by Heid is an antifoaming agent and that the claims are anticipated. Applicants respectfully traverse.

This rejection is improper for the same reason as the rejection discussed above for Li, namely that nothing in the cited website states or even hints that glycerol is an-antifoam reagent. Accordingly, Heid fails to teach each and every element of the rejected claims and the rejection should be withdrawn.

Rejections Under 35 U.S.C. §103(a)

Applicants address the rejections in the order set forth in the office action.

Blaschke in view of both Stemmer and Varadaraj, as evidenced by Swerdlow.

Claims 1-4, 7, 11, 15-18, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blaschke in view of both Stemmer and Varadaraj, as evidenced by Swerdlow .

Specifically, the Examiner asserts that Blaschke teaches real-time RT-PCR methods but does not teach use of detergents or anti-foam reagents. Stemmer is cited as providing the motivation to add detergents and antifoam reagents Varadaraj is cited as teaching that detergents improve the specificity of the amplification process. Swerdlow is cited as teaching that air bubbles interfere with microfluidic technology and that detergents create air bubbles. Based upon this combination of no less than four references, the Examiner concludes that the claimed invention would have been *prima facie* obvious. Applicants respectfully traverse.

When combining references to make out a *prima facie* case of obviousness, the examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion/motivation to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *see also* MPEP §§ 2142-43 (August 2001). Thus, the examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002). In the instant case, the Examiner has failed to describe why one of ordinary skill in the art would have been motivated to combine the cited references, and has failed to provide appropriate evidence that there was a reasonable expectation of success in making the combination. Accordingly, no p*rima facie* case of obviousness exists and the rejection should be withdrawn.

First, although Varadaraj may suggest that in certain circumstances certain detergents may be added to a PCR, it also states that ethanol *inhibited* PCR amplification. The www.dermaxime.com/alcohol.htm website cited by the Examiner states that ethyl alcohol (ethanol) is an antifoam[1]. This result confirms the findings in the present application, namely that certain antifoams are deleterious in PCR reactions. Accordingly, Varadaraj teaches that addition of an antifoam is deleterious to PCR and therefore teaches directly away from the instantly claimed invention. Indeed, Varadaraj confirms the surprising nature of the results obtained by the applicants that certain antifoams at particular concentrations can be used in PCR reactions without substantially inhibiting the reaction.

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[1] While www.dermaxime.com/alcohol.htm specifically states that ethanol is an antifoam, it does not suggest, as described above, that all alcohols inherently have antifoam properties.

Second, it is not at all clear what causes the bubbles in the method described by Swerdlow. Nothing in Swerdlow mentions that a detergent was used in the described method, so the source of the bubbles is a mystery. The bubbles could well have been generated after the PCR reaction during the liquid flow from the PCR reaction to the chromatography column and in that case there would have been no motivation whatsoever to add an antifoam to the PCR reagent. Moreover, if it was so obvious to use an antifoam to prevent bubbles, why did Swerdlow not simply add an antifoam? Swerdlow's failure to teach or suggest use of an antifoam speaks volumes regarding the Examiner's arguments regarding obviousness.

Third, Blaschke describes PCR methods and specifically describes obtaining single band PCR products (see page 83, right hand column) so one of ordinary skill in the art would have had no motivation to modify the teachings of Blaschke in the manner posited by the Examiner, let alone have the motivation to add detergent to the PCR mixture. Fourth, Stemmer is not an enabling reference for at least the reasons described above and would not have taught or suggested the instantly claimed invention to one of ordinary skill in the art. Moreover, the actual results described by Varadaraj that the antifoam ethanol *inhibited* PCR clearly would have led one of ordinary skill in the art to conclude that Stemmer's vague recitations regarding additives that might or might not be useful in PCR were unreliable and non-enabling.

In sum, Varadaraj clearly teaches away from the instant invention, and there would have been no motivation to combine Blaschke with any of the secondary references since Blaschke reports obtaining good results from PCR reactions in the absence of any foam-causing detergent or other source of foam. There is nothing in Swerdlow to indicate that there would have been any reason to add an antifoam to a PCR reaction, nor does Swerdlow teach or suggest that an antifoam would be a useful way of removing bubbles. Stemmer is non-enabling for all the reasons described above. Accordingly, nothing in the combination of references cited by the Examiner would have motivated one of ordinary skill in the art to use an antifoam reagent in a PCR reaction and no *prima facie* case of obviousness exists, and the rejection should be withdrawn.

Stemmer in view of Kyle.

Claims 1, 9, 11 and 13 were rejected as obvious over Stemmer in view of Kyle. Specifically, the Examiner asserts that Stemmer suggests using detergent and antifoam in a PCR

but fails to teach or suggest use of 1520-US as the antifoam. Kyle is cited as teaching that 1520-US is an antifoam. Applicants respectfully traverse.

Stemmer is a non-enabling reference for the reasons described above. Moreover, Kyle deals with fermentation, not PCR, and there would have been no motivation to combine these two disparate references. Why would one of skill in the art have been motivated to refer to a patent describing fermentation methods to identify a solution to a problem with a PCR reaction? Moreover, there is nothing in either Stemmer or Kyle that would have provided one of ordinary skill in the art with a reasonable expectation of success in using *any* antifoam, let alone 1520-US in a PCR reaction. In fact, Varadaraj's teachings regarding the deleterious effect of adding the antifoam ethanol in a PCR reaction would have led one of ordinary skill in the art to conclude that antifoams should not be used in PCR reactions. Accordingly, no *prima facie* case of obviousness exists and applicants respectfully request withdrawal of the rejection.

Stemmer and Kyle further in view of the Sigma catalog and Wierenga.

Claims 1, 8, 10-12 and 14 were rejected as obvious over Stemmer and Kyle further in view of the Sigma catalog and Wierenga. Specifically, Stemmer and Kyle are cited for the same propositions as above, but do not describe using combinations of antifoams. The Sigma catalog is cited as suggesting that antifoams can be used in combination and Wierenga is cited as teaching that a combination of the silicone and organic antifoams are synergistic. The Examiner asserts that it would have been obvious to combine the cited references to arrive at the instantly claimed invention. Applicants respectfully traverse.

The deficiencies of Stemmer and Kyle are set forth below and are not cured by either the Sigma catalog or Wierenga. Neither the Sigma catalog nor Wierenga teach or suggest that antifoams might be useful in a PCR reaction. In particular, one of ordinary skill in the art would not have been motivated to consult Wierenga, which deals with the problem of foaming when using household dishwasher detergents in high concentrations, in an attempt to solve a problem in a PCR reaction that uses different detergents at vastly lower concentrations. Even if the Sigma catalog shows that combinations of antifoams can in certain circumstances be used, or Wierenga suggests certain combinations of antifoams, neither of these references provides any motivation to use these combinations in a PCR reaction, nor provide any indication that the

combination would be successful. Accordingly, no *prima facie* case of obviousness exists and the rejection should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully submit that the claims are in condition for allowance and request a prompt notification to this effect.

Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).**

Respectfully submitted,

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Date: October 12, 2006

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